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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-524/S-005

Pharmacology Review(s)

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REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Key words:
Reviewer Name: Kumar D. Mainigi
Division Name: Dermatologic and Dental Drug Products, HFD-540
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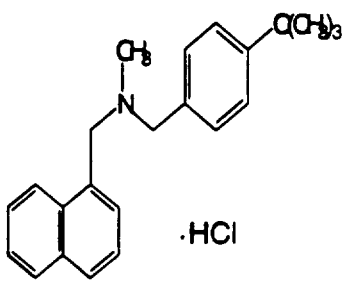
NDA 20-524/SE1-005/08-07-000
Information to sponsor: None
Sponsor: Bertek Pharmaceuticals, Inc.
Research & Development Division
320 Lakeside Drive, Suite A
Foster City, CA 94404
Manufacturer:

Drug: Mentax® (butenafine HCl cream) Cream 1%
Code Name: KP-363
Chemical Name: *N*-4-*tert*-Butylbenzyl-*N*-methyl-1-naphthalenemethylamine Hydrochloride
Molecular Formula/Molecular Weight: $C_{23}H_{27}N.HCl/353.93$



Butenafine HCl

Drug class: Antifungal
Indication: Treatment of Tinea versicolor

Relevant submissions: INDs:

NDAs: 20-524: Mentax (butenafine HCl) Cream 1% for the treatment of tinea pedis (approved 10/18/96)
20-663: Mentax (butenafine HCl) Cream 1% for the treatment of tinea corporis and tinea cruris (approved 12/31/96)

Route of administration: Topical

Clinical formulation: Butenafine HCl Cream 1% (PDC-010-C-003)

Ingredients	Percentage (w/w)
Purified water USP	
Propylene glycol dicaprylate	
Glycerine USP	
Cetyl alcohol NF	
Glyceryl monostearate	
White petrolatum USP	
Stearic acid NF	
Polyoxyethylene cetyl ether	
Butenafine HCl	1.00
Benzyl alcohol NF	
Diethanolamine NF	
Sodium benzoate NF	

Disclaimer: The information submitted by the sponsor is utilized to prepare this review.

Proposed clinical use: In this Clinical Efficacy Supplement of approved NDA 20-524, the sponsor has proposed to use butenafine HCl cream 1% for the treatment of tinea versicolor. The patients will receive one daily application of the drug product (24mg/m^2) for two weeks. The same dosing regimen was approved for the treatment of tinea cruris and tinea corporis under NDA 20-663 in 1996.

Previous human experience and drug history: Butenafine HCl cream 1% for the treatment of interdigital tinea pedis, tinea corporis, and tinea cruris has been marketed under the trade name Mentax^R (butenafine HCl cream) Cream 1% in Japan since 1992, and in USA since 1996.The same formulation is marketed in Canada under the trade name Dr. Scholl's^R Athlete's Foot Cream since April 1997.

Non-clinical studies: No new non-clinical studies were requested or required to support the safety of this already approved drug product.

Overall summary of Pharmacology and Toxicology: Since review of its first drug application (IND Butenafine HCl Cream 1%), butenafine HCl has been extensively evaluated in cream, optimized cream, gel, nail gel, and oral formulations in a wide spectrum of *in vivo* and *in vitro* studies in multiple species.

In a guinea pig model for experimental dermatomycosis, ten daily oral doses (10 and 40 mg/kg) of drug were efficacious both in reducing the intensity of infection as well as providing a significant cure.

The administration of single oral dose (5, 20, and 100 mg/kg) to dogs did not affect the cardiovascular parameters such as systolic and diastolic and mean arterial blood pressures, heart rate, QA, P-R, QRS, R-R intervals, and electrocardiograms.

The subcutaneous (1-100 mg/kg) and the topical (0.3-3% solutions) doses of butenafine HCl to guinea pigs and mice did not affect the somatic, and central and autonomic systems, respectively.

Intravenous administration of drug (1, 10, and 100 mg/kg) to dogs caused a slight increase in the respiratory rate at the highest dose level.

An oral dose of 25mg butenafine HCl/kg to rats produced a marked ($p<0.01$) decrease in percent gastric emptying, however, no effect was observed at 1 and 5mg/kg dose levels. In mice, the drug did not affect the intestinal transport when treated with oral doses up to 100mg/kg.

In a single oral dose (5, 25, and 100mg/kg/day) study in a rat model for Irwin test, butenafine did not affect any behavioral or physiological parameters.

In a mice subcutaneous study, at dose levels ranging from 1 to 100mg/kg/day for six weeks, drug had no affect on the coagulation process. Also no hemolysis or changes in the plasma pharmacokinetics were observed in rabbit blood cells treated *in vitro* with 10^{-4}M butenafine HCl.

The daily subcutaneous doses of 1-25mg butenafine HCl/kg/day for six weeks produced no change in the levels of various hormones in rats, however, at the highest dose level, a slight hypertrophy of the adrenal glands was observed in females.

The oral LD_{50} in rats, mice, and dogs exceeded 5g/kg. The intravenous and subcutaneous LD_{50s} in mice were >140 and >200 mg/kg, respectively; the corresponding values in rats were >100 and >150mg/kg. The primary systemic adverse effects of acute oral doses (up to 5000mg butenafine HCl/kg) in mice, rats, and dogs included decrease in body weight, soft feces, diarrhea, rough coats, and hunched posture. All animals had whitish diarrhea resembling the dosing material. In dogs, in addition to whitish vomitus, changes in some urinary parameters were also observed. Following the intravenous (0-140mg/kg) or subcutaneous (0-200mg/kg) doses, rodents at the highest dose level showed a dose-related decrease in gain in body weights, reduced mobility in the high-dose rats, and erythema or swelling at the site of administration. All adverse effects were reversed

during the 14 days observation period. At necropsy, no drug-induced gross lesions were found.

Following seven daily oral doses (up to 1500mg/kg/day), of butenafine HCl to rats, a decreased gain in body weight, increased weights of liver, kidneys, and adrenals, and reduced weights of thymus, heart, and spleen, were observed at 500 and 1500mg/kg dose level. The macroscopic lesions in a few highest-dose rats included distended, impacted stomachs, and small prostate and thymus. In beagle dogs, seven daily oral doses (1-500mg/kg) of drug caused decrease in food consumption, body weights and physical activity.

In a 28-day oral (5-320 mg/kg/day) toxicity study in rats, the significant drug related changes at 80 and 320 mg/kg levels included decreased body weights, and increased weights of liver and kidneys, however, the related histopathologic changes were observed only in the liver. These lesions included hepatocyte hypertrophy, hepatocyte necrosis, and mixed inflammatory infiltrates in 80mg/kg females and in both sexes at 320mg/kg level. The electronmicroscopic examination of liver revealed more pronounced microsteatosis in the males than females of the highest dose group. There was no evidence for peroxisome proliferation. The microscopic lesions in the lungs included histiocytic infiltrates in females of 320mg/kg group. The NOAELs of 80 and 20mg/kg/day were established in male and female rats, respectively.

In a parallel 28-day oral toxicity study (5-1000mg/kg/day) in beagle dogs, blue/pale mucous membranes, vomitus, decreased activity, and salivation observed within two hours of dosing were restricted to the high–dose groups. At the time of dosing, tremors and convulsions were also observed in two males of this group. The drug-related lesions also restricted to the males in the 1000mg/kg group included the bone marrow hypocellularity, albuminous degeneration and hepatocyte vacuolation in the liver, and lymphoid depletion in the lymph nodes and thymus. The electronmicroscopic examination revealed moderate to marked microsteatosis in males and females of 1000mg group. A slight increase in the amount of smooth endoplasmic reticulum was observed at 160 and 1000mgkg/day levels. There was no evidence for peroxisome proliferation. The NOAEL for both the sexes was considered to be 160mg/kg/day.

Following subcutaneous injections of butenafine HCl to rats at doses up to 25mg/kg/day for three months, and at 5mg/kg for six months, the local reactions included thickening of the skin and nodule formation at the site of drug administration. These changes were associated with microscopic lesions of intradermal hemorrhage and abscess. The severity of these lesions was markedly reduced during the one-month recovery period. The clinical signs for systemic toxicity restricted to the high-dose groups included decreased body weights and food consumption, changes in a few clinical pathology parameters, and

increased weights of liver and spleen. According to the study author, such nonspecific effects are frequently associated with exposure to allylamines.

The subcutaneous doses of 0.25, 2.5, or 25.0mg/kg butenafine HCl administered to rats prior to mating, during the mating period, and through seventh day of pregnancy, did not produce any change in fertility. The same subcutaneous doses administered during the organogenesis period caused no maternal toxicity, or changes in fetal development. Similarly, no changes in sexual maturity, reproductive function, or postnatal differentiation were observed at the same subcutaneous doses administered during the perinatal and postnatal periods. In an oral (960, 2,400, and 4,800mg butenafine HCl/m^2) teratogenicity study in rabbits, no treatment-related external, visceral, or skeletal malformations or variations were observed.

In two *in vitro* tests (Ames reverse mutation, and chromosomal aberration assays in Chinese hamster lymphocytes) and *in vivo* micronucleus assay in rats indicated that butenafine HCl was nonmutagenic and nonclastogenic.

The butenafine HCl Optimized Cream 1% tested as a mild dermal irritant in a rabbit primary irritation test. However, the same formulation produced no ocular irritation in rabbits.

Butenafine tested negative in a photosensitization test in rats and guinea pigs. None of the butenfine formulations at 1% strength were phototoxic to guinea pigs.

One hour after the administration of a radioactive oral (0.2mg/kg) or subcutaneous dose (1mg/kg) of butenafine HCl, approximately 1.5-3% of the administered radioactivity appeared in the plasma. It was determined that >90% of this radioactivity was bound to the serum proteins. A biphasic elimination of butenafine with a terminal half-life ranging from 15 to 36 hours was recorded. It was suggested that the long half-life be related to a significant distribution of drug, and its slow elimination from the adipose tissue.

Following the administration of 7 daily oral doses to rats (1-1500mg/kg/day) and dogs (1-1200mg/kg/day), only after the last dose, the parent drug and its metabolites in the plasma were detected at all dose levels. In rats, the largest amount of ~6 ug/mL was detected at 8 hours post-dose in females of the highest dose group. The highest amount of ~8 ug/mL was found in a male dogs of 1200mg/kg group at one hour post-dose after dose 7. However, no dose-related trend was observed in either of the species.

After 28 daily oral doses of butenafine HCl (5-320mg/kg/day), no dose, time, or sex-related trends were observed in rats. The highest amount of ~6ug/mL of butenafine was detected at 8 hours post-dose after the first dose in one male of the highest dose group. The plasma concentration of drug and its metabolites in the highest dose group ranged

from 1-6ug/mL after the first dose; the values after the last dose ranged from 1 to 5ug/mL. The corresponding values at the next lower dose level (80mg/kg) ranged from 1-2ug/mL after the first as well as after the last dose.

After a single oral radioactive dose to rats, approximately 3% of the administered dose (0.2mg/kg) was absorbed, however, less than 0.03% of the parent drug was found in the plasma within 4 hours of dosing, indicating a significant first-pass metabolism. It is predicted that butenafine has some inhibitory effect on the cytochrome P-450 drug metabolizing enzymes. The parent drug, rapidly metabolized by methylation, dealkylation, and hydroxylation, is not detected in the liver, bile, and urine. The analysis of hydrolyzed samples of bile and urine indicated extensive conjugation of three known metabolites. In the 7 and 28-day oral rat studies, three well characterized metabolites, 1-napthoic acid, N-4- (2-hydroxy-1,1-dimethyl)-benzyl-N-methyl-1-naphthalenemethylamine, and naphthyoylglycine, and two unknown metabolites (UNK1 and UNK2) of butenafine were found. The level of the major metabolite (1-napthoic acid) in the plasma ranged between 1 to 100% of the administered parent drug.

Butenafine and its metabolites were primarily found in the gut, liver, pancreas, and adrenals of rats. About 60% of the administered dose was found in the bile, almost entirely in the form of conjugated metabolites. A low level of drug is transferred through the placenta, however, the tissue distribution of drug in the fetus was similar to the maternal distribution.

Butenafine is extensively excreted in the milk, reaching a peak level six-fold greater than the plasma level within three hours of a single subcutaneous dose.

Labeling: The label approved under NDAs 20-524 and 20-663 has been modified according to the current format of CDER.

Carcinogenesis, Mutagenesis, Impairment of Fertlity

Long-term studies to evaluate the carcinogenic potential of Mentax^{R} Cream 1% have not been conducted. Two *in vitro* assays (bacterial reverse mutation test and chromosome aberration test in Chinese hamster lymphocytes) and one *in vivo* study (rat micronucleus bioassay) revealed no mutagenic or clastogenic potential for butenafine. In subcutaneous reproductive studies in rats at 25mg/kg/day (6 times the maximum possible systemic dose in humans based on a mg/m^2 comparison) dose level, butenafine did not produce any adverse effects on male or female fertility.

Pregnancy

Teratogenic effects: Pregnancy Category B

Subcutaneous or topical doses of butenafine (25 to 50mg/kg/day) (equivalents to 5 to 20 times the maximum possible systemic dose in humans based on a mg/m^2 comparison) were not teratogenic in rats and rabbits. In an oral teratogenicity study in rabbits (80, 200, and 400mg butenafine HCl/kg/day) (equivalent to 3 to 16 times the maximum possible systemic dose in humans based on a mg/m^2 comparison), no treatment-related external, visceral, or skeletal malformations or variations were observed. There are, however, no adequate and well-controlled studies that have been conducted with topically applied butenafine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Interpretation of safety data: In animal studies, butenafine has been safely evaluated at 1% to10% concentration levels, indicating margin of safety ranging from 6 to 42 times (mg/m^2) the maximum recommended topical human dose The proposed dosing regimen (one daily application for two weeks) for the treatment of tinea versicolor is identical to that approved for the treatment of tinea corporis and tinea cruris. The adverse effects observed in the clinical studies with butenafine HCl cream 1% included burning/stinging, itching, and worsening of the condition. None of these lesions are considered serious or life threatening.

Regulatory conclusion: The addition of a new indication will not change the well-established margin of safety for butenafine. It is fairly safe to use the proposed dosing regimen for the treatment of tinea versicolor.

Regulatory recommendations: None at this stage.

/S/

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CC: NDA 20-524
HFD-82
HFD-540
Pharm/Mainigi
MO/Vaughan
Chem/Pappas
CSO/Cross

Concurrence:
A.Jacobs-TL/HFD-540 /S/
J.Wilkin-Dir/HFD-540